CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.5511074

Available online at: http://www.iajps.com *Research Article*

A PROSPECTIVE OBSERVATIONAL STUDY ON EFFICACY OF HEPATOPROTECTIVE DRUGS IN IN-PATIENTS WITH ALCOHOLIC LIVER DISEASE IN A TERTIARY CARE TEACHING HOSPITAL

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Article Received: July 2021 **Accepted:** August 2021 **Published:** September 2021

Abstract:

Aims and objectives: *The study was carried out with an aim to evaluate the efficacy of the hepatoprotective drugs prescribed to the patients. This might help in designing better treatment plans for the patients suffering from the alcoholic liver disease. The dose effectiveness can be analysed for appropriate dosing frequency of the prescribed drugs for better treatment plan and improving the quality of life and providing better health care to the society.*

Methodology: *The study was carried out in a tertiary care teaching hospital on 100 subjects admitted in the hospital (in-patients). The study was carried out for a period of 6 months. During this period, different patients suffering from the alcoholic liver disease were identified and their disease conditions were monitored and the levels of aspartate transaminase, alanine transaminase and serum bilirubin levels were checked after repeated dosing of the drugs during the course of treatment.*

Results: *The patients were divider based on gender, age, duration of intake of alcohol and the type of alcoholic liver disease they suffer from. It was seen that the males are more prone to the disease than female due to increased alcohol consumption. Binge alcohol intake for more than 5-10 years can cause serious damages to the liver. After repeated drug administration, the blood levels for Aspartate transaminase and Alanine transaminase and serum bilirubin were checked and it was noted that there was a significant improvement in the levels of these enzymes in the blood when both Rifaximin and Ursodeoxycholic acid were administered in combined form at a dose of 550mg and 300mg respectively.*

Conclusion: *In our study we conclude that the extent of damage caused to the liver due to alcohol consumption can be controlled and further damage can be prevented by providing appropriate treatment measures using drugs and other preventive measures along with strict abstinence of alcohol.*

Keywords: Alcoholic Liver Disease, *Rifaximin, Ursodeoxycholic acid*

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Please cite this article in press Mohammed Majid Iqbal et al, ***A Prospective Observational Study On Efficacy Of Hepatoprotective Drugs In In-Patients With Alcoholic Liver Disease In A Tertiary Care Teaching Hospital*** *., Indo Am. J. P. Sci, 2021; 08(9).*

INTRODUCTION:

Alcoholic Liver Disease is a term that encompasses the liver manifestations of alcohol overconsumption. Excessive alcohol use can cause: fatty liver, alcoholic hepatitis, cirrhosis. Alcoholic cirrhosis is responsible for about 40% of the deaths due to cirrhosis. Patients often deny the excessive usage of alcohol. Severe forms of disease (hepatitis, cirrhosis) are associated with ingestion of 160 g/d for 10–20 years; women more susceptible than men and can develop advanced liver disease with less alcohol intake. Hepatitis B and C may be cofactors in the development of liver disease. Malnutrition may contribute to development of cirrhosis.

Pathophysiology [2]

The mechanism behind this is not completely understood. 80% of alcohol passes through the liver to be detoxified. Chronic consumption of alcohol results in the secretion of pro-inflammatory cytokines (TNF-alpha, Interleukin 6 [IL6] and Interleukin 8 [IL8]), oxidative stress, lipid peroxidation, and acetaldehyde toxicity.

These factors cause inflammation, apoptosis and eventually fibrosis of liver cells. Occurrence of this in only a few individuals is still unclear. Additionally, the liver has tremendous capacity to regenerate and even if 75% of hepatocytes are dead, it still continues to function as normal.

Fatty liver is the accumulation of fatty acids in liver cells. These are seen as fatty globules under the microscope. Alcohol consumption causes development of large fatty globules throughout the liver and can begin to occur after a few days of heavy drinking. Alcohol is metabolized by alcohol dehydrogenase (ADH) into acetaldehyde, which is then further metabolized by aldehyde dehydrogenase (ALDH) into acetic acid, and is finally oxidized into carbon dioxide (CO_2) and water (H_2O). This process generates NADH, and increases the NADH/NAD+ ratio. A higher NADH concentration induces fatty acid synthesis while a decreased NAD level results in decreased fatty acid oxidation. Subsequently, the higher levels of fatty acids signal the liver cells to compound it to glycerol to form triglycerides. This accumulation of triglycerides leads to the condition of fatty liver.

Alcoholic hepatitis is characterized by the inflammation of hepatocytes. Between 10% and 35% of heavy drinkers develop alcoholic hepatitis. The development of hepatitis is not directly related to the dose of alcohol, some people seem more prone to this reaction than others. This is called alcoholic steatosis necrosis and the inflammation appears to predispose to fibrosis in liver. Inflammatory cytokines (TNF-alpha, IL6 and IL8) are thought to be essential in the initiation and perpetuation of liver injury by inducing apoptosis and necrosis. One possible mechanism for the increased activity of TNF-α is the increased intestinal permeability due to liver disease. This facilitates the absorption of the gut-produced endotoxin into the portal circulation. The Kupffer cells of the liver then phagocytose endotoxin, stimulating the release of TNF-α. TNF-α then triggers apoptotic pathways through the activation of caspases, resulting in cell death.

Cirrhosis is a late stage of serious liver disease marked by inflammation, fibrosis (cellular hardening) and damaged membranes preventing detoxification of chemicals in the body, ending in scarring and necrosis (cell death). About 10% to 20% of heavy drinkers will develop cirrhosis of the liver. Acetaldehyde may be responsible for alcohol-induced fibrosis by stimulating collagen deposition by hepatic stellate cells. The production of oxidants derived from NADPH oxidase and/or cytochrome P-450 2E1 and the formation of acetaldehyde-protein adducts damage the cell membrane. Symptoms include jaundice (yellowing), liver enlargement, and pain and tenderness from the structural changes in damaged liver architecture. Without total abstinence from alcohol use, cirrhosis will eventually lead to liver failure. Late complications of cirrhosis or liver failure include portal hypertension (high blood pressure in the portal vein due to the increased flow resistance through the damaged liver), coagulation disorders (due to impaired production of coagulation factors), ascites (heavy abdominal swelling due to build-up of fluids in the tissues) and other complications, including hepatic encephalopathy and the hepatorenal syndrome.

Diagnosis: [3]

The diagnosis of ALD can generally be made based on clinical and laboratory features alone in patients with a history of significant alcohol consumption after other aetiologies for chronic liver disease have been ruled out. However, the diagnosis of ALD can be clinically challenging as there is no single laboratory or imaging study that can confirm the diagnosis. Furthermore, patients may be completely asymptomatic, have no clinical signs of early ALD or early cirrhosis and may have normal liver enzymes. In addition, patients may have co-existing risk factors for non-alcoholic fatty liver disease such as obesity and diabetes and some may not be entirely

forthcoming as to their degree of alcohol consumption.

LABORATORY INVESTIGATIONS: [3]

A series of special blood tests can often determine whether or not the liver is functioning properly. These tests can also distinguish between acute and chronic liver disorders and between hepatitis and cholestasis. The most commonly performed blood tests include the following:

- **Alanine transaminase (ALT) test:** This test measures the level of alanine aminotransferase (an enzyme found predominantly in the liver) that is released into the bloodstream after acute liver cell damage. This test may be performed to assess liver function, and/or to evaluate treatment of acute liver disease, such as hepatitis. In an healthy individual it ranges for upto 35 units/lt.
- **Aspartate transaminase (AST) test:** This test measures the level of aspartate transaminase (an enzyme that is found in the liver, kidneys, pancreas, heart, skeletal muscle, and red blood cells) that is released into the bloodstream after liver or heart problems. In normal healthy individual, its value ranges between 0-35 units/lt.
- **Serum bilirubin test:** This test measures the levels of bilirubin in the blood. Bilirubin is produced by the liver and is excreted in the bile. Elevated levels of bilirubin may indicate an obstruction of bile flow or a problem in the processing of bile by the liver. The normal value ranges from 0.1-1 mg/dl.
- **Serum albumin test:** This test is used to measure the level of albumin (a protein in the blood) and aides in the diagnosis of liver disease. The normal value for a healthy individual ranges between 3.3-4.8 g/dl.
- **Prothrombin time (PTT) test:** The prothrombin time test measures how long it takes for blood to clot. Blood clotting requires vitamin K and a protein that is made by the liver. Prolonged clotting may indicate liver disease or other deficiencies in specific clotting factors.

  Any deviation from the normal ranges is considered as a mark for malfunctioning liver, and thus can be further used to estimate the extent of liver damage.

TREATMENT: [4]

Abstinence: This can help to reverse some early stages of liver disease. For example, stopping drinking once diagnosed with fatty liver disease may be able to reverse the condition within 2 to 6 weeks trusted Source.

Once a person is diagnosed with alcoholic liver disease at any stage, it is recommended to never resume drinking. Any conditions that have reversed will typically return once drinking restarts.

As alcohol dependency can make it more difficult to quit drinking alcohol, it is necessary to gradually reduce alcohol intake.

Those who regularly drink more than the recommended daily limits of alcohol should not stop drinking without medical support. Withdrawal from alcohol can be life-threatening. Individuals should seek help from a medical professional to safely manage alcohol withdrawal.

The recommended daily limits are more than one drink a day for women and more than two drinks a day for men.

Lifestyle changes

Weight loss and quitting smoking might also be recommended since being overweight and smoking have both demonstrated a role trusted Source in making alcoholic liver disease worse. Taking a daily multivitamin is usually recommended as well.

Medications:

I. Corticosteroids

Corticosteroids have been the most extensively studied form of therapy for AH, but their role remains limited. The rationale for steroid use is to decrease the immune response and pro-inflammatory cytokine response. A major disadvantage to corticosteroids is their lack of applicability in many patients with AH.

II.Pentoxifylline

Pentoxifylline (PTX) is a nonselective phosphodiesterase inhibitor which increases intracellular concentrations of adenosine 3, 5′-cyclic monophosphate (cAMP) and guanosine 3′,5′-cyclic monophosphate (cGMP), and decreases production of pro-inflammatory chemokines cytokines including tumour necrosis factor (TNF). Pentoxifylline is regularly used in patients with AH and alcoholic cirrhosis because of its anti-inflammatory properties, its protective effects against hepatorenal syndrome and its excellent safety profile.

III. Ursodeoxycholic acid

Ursodiol (commonly known as ursodeoxycholic acid) is a product of metabolism of bacteria in the intestine. It is considered a secondary bile acid. Ursodeoxycholic acid reduces elevated liver enzyme levels by facilitating bile flow through the liver and protecting liver cells. The main mechanism if anticholelithic. Although the exact process of ursodiol's anticholelithic action is not completely understood, it is thought that the drug is concentrated in bile and decreases biliary cholesterol by suppressing hepatic synthesis and secretion of cholesterol and by inhibiting its intestinal absorption.

Generally prescribed dose is 300mg twice daily after food.

IV. Rifaximin

Rifaximin is an antibiotic which works within the gastrointestinal system. It is given to help prevent episodes of a problem called hepatic encephalitis in people with liver disease. Hepatic encephalitis can cause a range of symptoms. These include confusion, personality changes, and changes in alertness.

Generally prescribed dose of rifaximin is 550mg once daily.

AIMS AND OBJECTIVE:

The aims and objective for the conduct of this observational study is

- To evaluate the efficacy pattern of the prescribed hepatoprotective drugs on liver functions in the patients.
- To evaluate the prevalence of alcoholic liver disease.
- To evaluate the effectiveness of hepatoprotective agents in alcoholic liver disease.
- To observe the dose and frequency of the prescribed hepatoprotective drugs to the patients in tertiary care teaching hospital.
- To assess the quality of life of the patients.

NEED OF THE STUDY: [16]

Alcohol is the leading cause for liver disease accounting for about 10 Lakhs new cases every year being reported in India. The outcome of alcohol related liver disease is determined largely by patient alcohol consumption patterns. About 50% of patients manage to abstain or at least reduce their alcohol intake to a significant amount while the remaining continues to drink. It is been suggested that the drugs capable of preventing damage to the liver due to alcohol intake or limiting and repairing the damage already sustained might play an important role in managing alcoholic patients. A number of drugs with hepatoprotective role are available as the so called hepatoprotective drugs and are used on a broad scale. However, the evidence of their use without abstinence leading to any benefit are very poor.

METHODOLOGY:

Study Site: Department of General Medicine, Osmania General Hospital – a tertiary care teaching Hospital, Hyderabad.

Study Design: A Hospital based Prospective Observational study.

Study Period: 6 months

Sample size: 100 patients.

Inclusion criteria:

- Patients of above 18 years of age.
- Patients of both the genders.
- Alcoholic in-patients, admitted into the hospital.

Exclusion criteria:

- Patients below 18 years of age.
- Out patients visiting hospital.
- Pregnant and lactating women.
- Patients with other comorbid cardiac disorders, drug induced liver disorders etc.

PLAN OF WORK:

The observational study was being carried out at the department of general medicine in the tertiary care teaching hospital. The patients diagnosed with alcoholic liver disease were taken into the study protocol, and their blood reports were being analysed before and after the administration of medicines as per the prescribed plan.

The study plan includes:

- Data collection forms were designed for recording the patient data.
- Based on the requirement of the study objectives, the subjects were identified.
- The patients were being interrogated and their demographic data, previous medication and disease history were collected.
- The important physiological parameters of the patient like serum aspartate transaminase levels, alanine transaminase levels, serum bilirubin levels etc were recorded.
- The prescribed pharmacotherapy was recorded and the patient was followed up on daily basis.
- The liver function test reports were been analysed at various stages of treatment.
- Observations were recorded in the designed data collection form.

- Analysing the, conclusion to be drawn and decisions to be taken.

RESULTS:

Table.1: DISTRIBUTION OF SUBJECTS BASED ON AGE -GROUPS

AGE GROUP	NO. OF SUBJECTS	PERCENTAGE
20-30	18	18%
30-40	43	41%
40-50	20	20%
50-60	12	12%
60 – 70	07	07%

The above table states that the total patient population taken under the study was divided into different age groups starting from 20 years of age, with an interval of 10years. It was found that the patients of 30-40 years age group were highly affected with alcoholic liver disease followed by those of 40-50 years age group.

Table.2: DISTRIBUTION OF SUBJECTS BASED ON GENDER

S.No	Gender	No. of subjects	Percentages
1	Male	88	88%
2	Female	12	12%

The table states that the total study population was divided based on their sex into male and females. It was observed that the males ae highly affected with the disease when compared to females which might be due to increased consumption of alcohol by men when compared to females. Increased social activity, socio economic stress might also be a triggering factor for the same.

Table.3: DISTRIBUTION OF SUBJECTS BASED ON INTAKE OF ALCOHOL IN YEARS

DURATION OF INTAKE	NO. OF SUBJECTS	PERCENTAGE
5 – 10	40	40%
11 – 15	21	21%
16 – 20	20	20%
21 – 25	12	12%
>25	07	07%

Table.4: DISTRIBUTION OF SUBJECTS BASED ON THE TYPE OF LIVER DISEASE

Type of disease	No of cases	Percentage
Alcoholic hepatitis	27	27%
Fatty liver	08	08%
COL	53	53%
Viral Hepatitis	12	12%

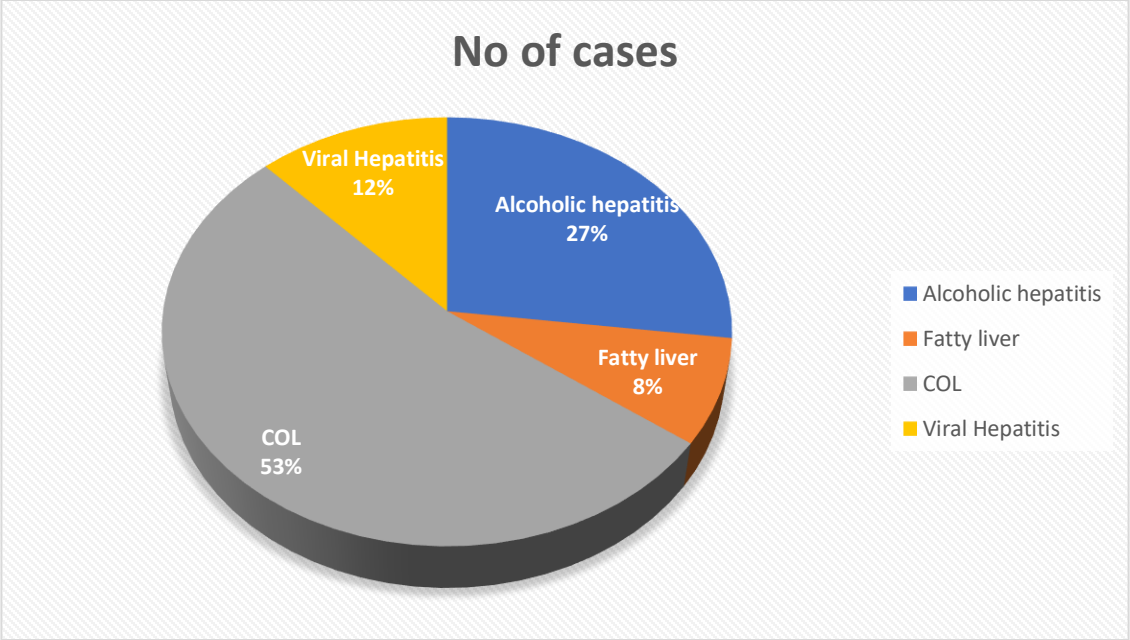

Fig.1: DISTRIBUTION OF SUBJECTS BASED ON THE TYPE OF LIVER DISEASE

The patients based on the category of disease were divided into 4 categories as alcoholic hepatitis, fatty liver, viral hepatitis and the last stage as cirrhosis of liver. During the study period it was found that most of the patients suffered from the chronic stage, the cirrhosis of liver i.e., out of the total population of 100 samples, 53 patients suffered from COL. Binge drinking of alcohol and other social habits trigger the conditions to worsen.

Table.5: DISTRIBUTION OF SUBJECTS BASED ON THE MEDICATION PRESCRIBED

MEDICATION PRESCRIBED	NO OF SUBJECTS	PERCENTAGE
URSODEOXYCHOLIC ACID	33	33%
RIFAXIMIN	11	11%
BOTH	56	56%
PENTOXIFYLLINE	0	0%

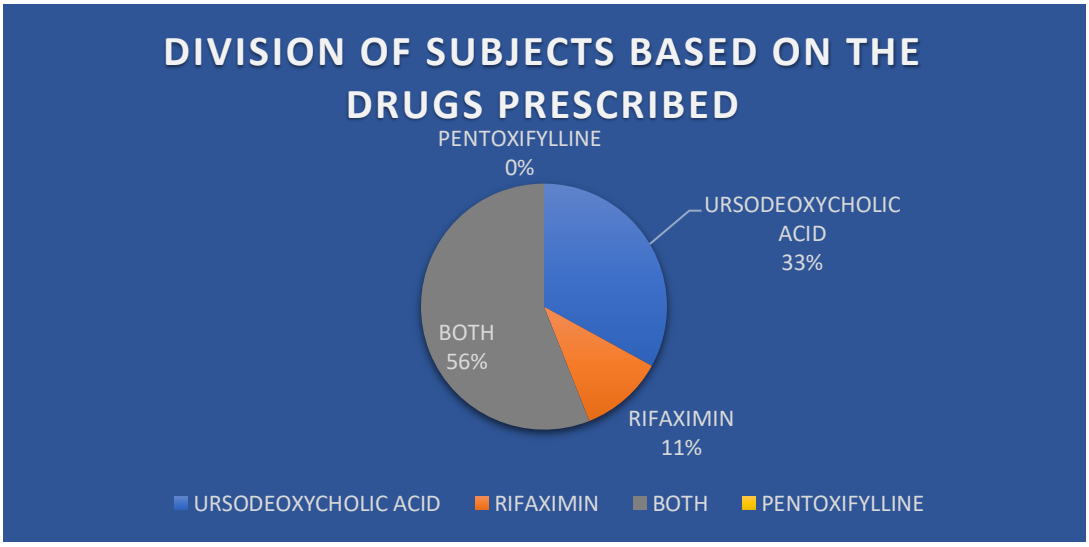

Fig.2: DISTRIBUTION OF SUBJECTS BASED ON THE MEDICATIONS PRESCRIBED.

During the course of study, it was observed the patients were treated using 3 drugs either as single drug regimen or in combination form. The drugs used were Ursodeoxycholic acid, Rifaximin and pentoxifylline. It was observed that most of the patients were treated using the combination of ursodeoxycholic acid at a dose of 300mg and Rifaximin at a dose of 550mg when compared to individual dosage regimen.

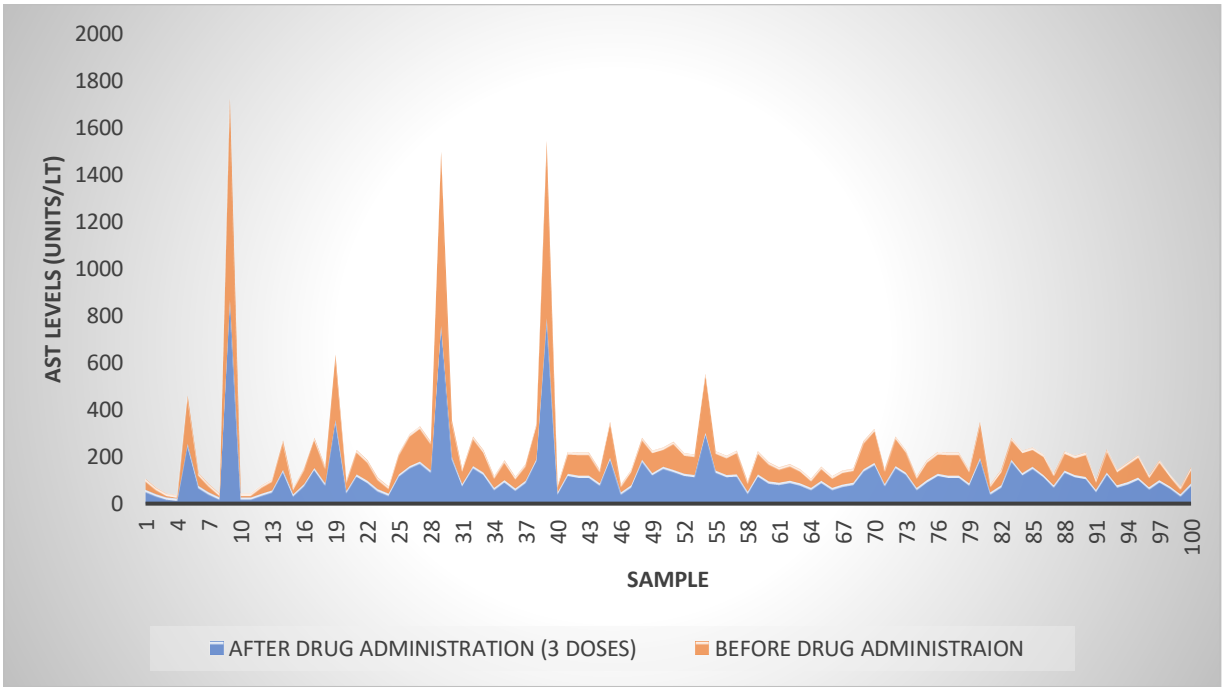

Fig.3: GRAPHICAL REPRESENTATION OF DRUG EFFECTS ON ASPARTATE TRANSAMINASE

Subjects were analysed based on their levels of aspartate transaminase (AST), after administration of 3 doses of the drugs, there was a decrease in the levels of the enzyme, showing the positive effects of the drugs. Decrease in the levels of enzyme in the blood indicative for an improvement in the condition of the patient

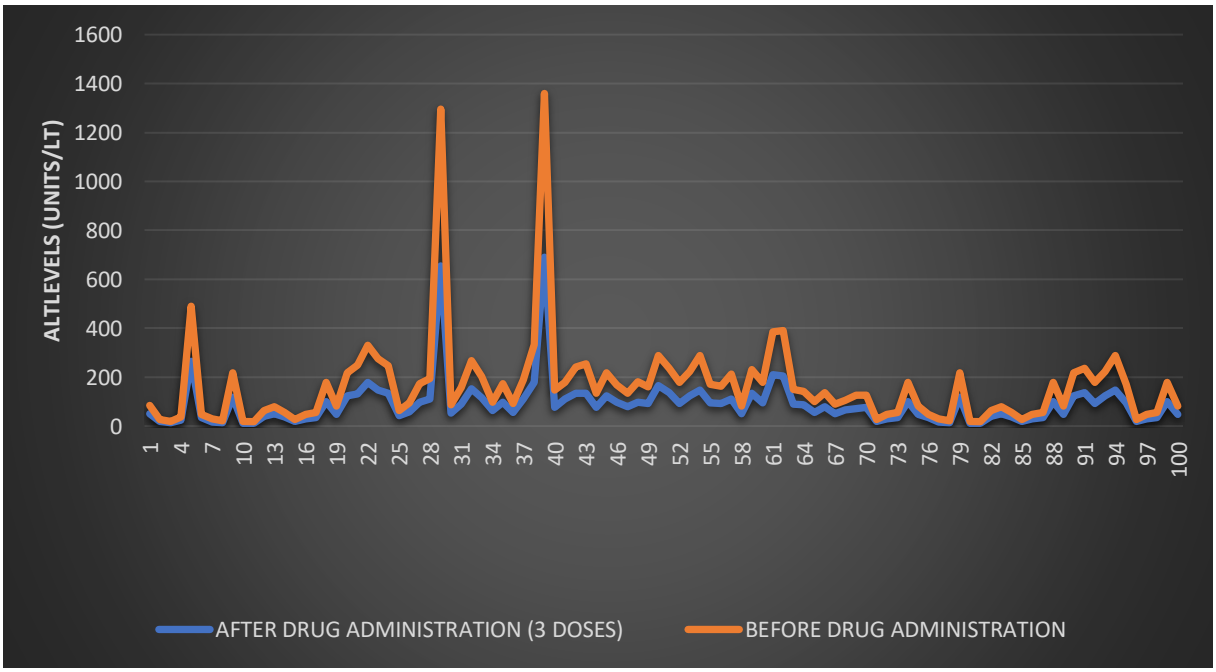

Fig.4: GRAPHICAL REPRESENTATION OF DRUG EFFECTS ON ALANINE TRANSAMINASE

Subjects were analysed based on their levels of Alanine Transaminase (ALT), after administration of 3 doses of the drugs, there was a decrease in the levels of the enzyme, showing the positive effects of the drugs. Decrease in the levels of enzyme in the blood indicative for an improvement in the condition of the patient

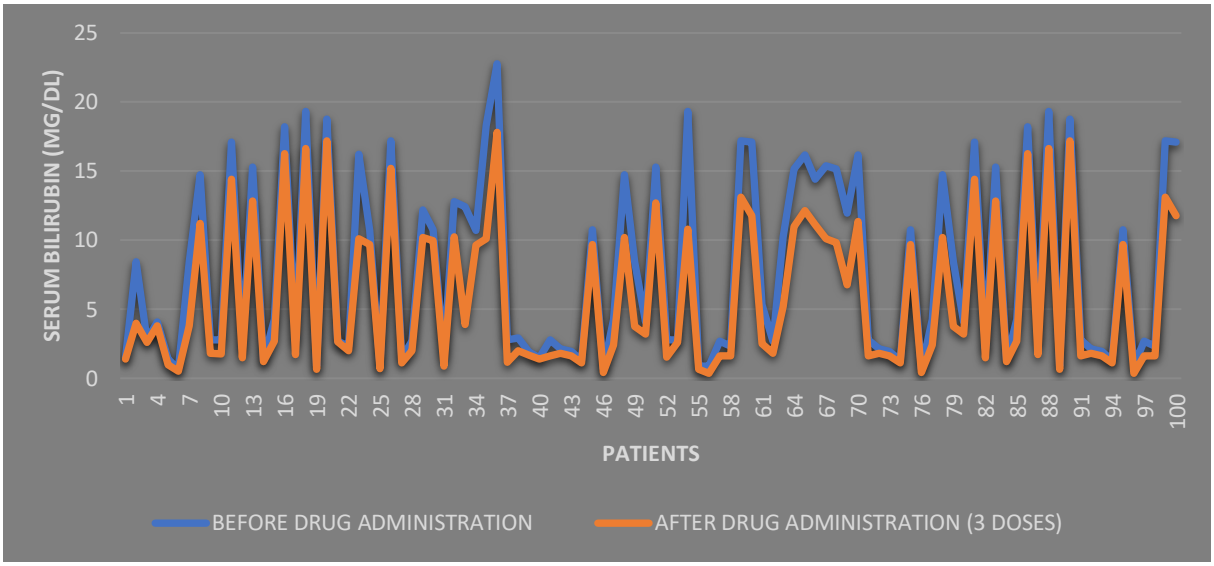

Fig.4: GRAPHICAL REPRESENTATION OF DRUG EFFECTS ON BILIRUBIN TOTAL LEVELS

Patients were observed both pre and post drug administrations. After the patients were administered with the drugs, after repeated doses it was observed that the patients showed a decrease in the levels of serum bilirubin when compared to the previous values before drug administration, showing positive drug effect and improvement in the liver conditions.

DISCUSSION:

- In countries like India where the population of backward classes is very high, alcohol consumption is the major cause for the liver damage and increased mortality. Alcoholic liver disease is caused in majority of patients who consume large quantity of alcohol on daily basis. There are no specific tests designated to diagnose the condition. However, it can only be ruled out by carrying various tests for liver function like SGOT, SGPT, Serum bilirubin levels estimations etc. Abnormally elevated levels of these enzymes mark the extent of liver damage caused. The SGOT/SGPT ratio also plays an important role in evaluation of liver injury. A ratio of more than 2 is considered to be a state of liver damage.
- Drugs like ursodeoxycholic acid (Udiliv, 300mg) and Rifaximin (Rifagut, 550mg) are mostly used in the treatment of the condition. Apart from these corticosteroids like prednisolone (40mg/day) and Pentoxifylline (400mg thrice daily) are also used.
- Apart from the drug therapy, abstinence of alcohol is the main precaution to be followed and is the main pillar for the treatment of the disease condition.

PATIENT COUNSELLING

The patients were counselled regarding to the disease conditions, medications to be taken and various other parameters like the Do's and don'ts during the treatment period and for the rest of the life for effective treatment. The important points discussed were:

- Abstinence of alcohol, as this plays the major role in treatment of liver disorders.
- Dietary measures to be taken. Don't eat foods high in fat, sugar and salt. Stay away from a lot of fried foods including fast food restaurant meals. Fibre rich meals are to be preferred.
- Strict medical compliance and regular follow up.

The patients were assessed on the basis of CAGE questionnaire. They include:

1. C: Have you ever felt you need to cut down your drinking habits?
2. A: Have people annoyed you by criticising your drinking habits?
3. G: Have you ever felt guilty about your drinking habits?
4. E: Have you ever had a drink of alcohol as the firsgt thing in the morning (eye opener)?

Each answer was awarded a score as 0 or 1 for yes and no respectively.

- Score of 0 or 1 indicates low risk drinking problem.
- Score of 2 or 3 indicates high doubt of alcoholism.
- Score of 4 is a diagnostic for alcoholism.

CONCLUSION:

Liver is one of the most important organs in the human body. It is mainly responsible for most of the internal body functions like protein synthesis, glycogen storage and detoxification of toxins. There is alteration seen in these functions when there is an injury caused to the liver due to a variety of reasons, alcohol consumption being one of them. Hence when any injury occurs to the liver it is mandatory to compensate the damage caused and prevent further deuteriation of the condition. Proper medicinal usage, complete abstinence of alcohol along with required lifestyle modifications can ease in the early treatment of the condition.

- The prospective observational study was carried out on a total of 100 subjects consisting of 88 males and 12 female patients for a duration of 6 months in a tertiary care teaching hospital.
- The patients were divided based on their gender, age, duration of intake of alcohol, the type of alcoholic liver disease they suffer, the medication prescribed during the course of treatment.
- The study shows that the patients of 30-40 years of age group were more prominent towards the disease due to increased alcohol consumption which might be due to variety of reasons like stress, socio economic factors etc.
- Upon observing the reports of the liver function tests like serum bilirubin, aspartate transaminase and alanine transaminase levels in the blood serum, before and after administration of drugs it was found that the patients have shown significant improvement in the blood reports.
- Damage caused to the liver cannot be reversed but the progression of damage can be slowed down and further damage can be prevented.
- Strict abstinence of alcohol, medication adherence and life style modifications can again help to lead a normal and healthy life.

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